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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,217	03/02/2004	Els A.J.M. Goulmy	2183-4285.1US	3284

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,217	GOULMY ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/02/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are pending.

2. Applicant's election without traverse of Group 8, claims 12-20 drawn to a process for producing cytotoxic T cells against a minor antigen, and a cytotoxic T cells produced by administering the isolated recombinant peptide comprising VLX-DDLLEA (SEQ ID NO: 1) wherein X is histidine or arginine to a mammal, filed 11/8/04, is acknowledged.

3. Claims 1-11 and 21 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 12-20 drawn to a process for producing cytotoxic T cells against a minor antigen, and a cytotoxic T cells produced by administering the isolated recombinant peptide comprising VLX-DDLLEA (SEQ ID NO: 1) wherein X is histidine or arginine to a mammal, are being acted upon in this Office Action.

5. The International Search Reports on PTO 1449, filed 3/2/04 have been considered but crossed out because the submission of International Search Reports are not appropriate to be printed on the issued patent.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a process for producing minor histocompatibility antigen HA-1 specific cytotoxic T cell providing an isolated, synthetic or recombinant peptide consisting the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X presents histidine or arginine and contacting an antigen presenting cell with the isolated, synthetic or recombinant peptide and thus producing the cytotoxic T cell, **does not** reasonably provide enablement for a process for producing a cytotoxic T-cell against *any* "minor antigen" as set forth in claims 12-15, 17-18 and 20, comprising

providing any isolated, synthetic or recombinant peptide "comprising" the sequence VLXDDLLEA (SEQ ID NO: 1), wherein X represents histidine or arginine, the process further comprising transducing the cytotoxic T-cell with any "suicide gene" as set forth in claim 16 and any cytotoxic T-cell produced by said method as set forth in claim 19. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo.

The specification does not teach how to make cytotoxic T cells against all "minor antigen" simply by providing any peptide "comprising" the sequence VLXDDLLEA wherein X represents histidine or arginine and contacting any "hematopoietic cell" with said peptide because of the following reasons.

First, the term "comprising" is open-ended. It expands the peptide to include amino acids at either or both ends. There is insufficient guidance as to which amino acids to be included and whether the resulting peptide would produce cytotoxic T cells against any or all-minor antigen. Stryer *et al*, PTO 1449, teach a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed relevant pages). Ngo *et al*, PTO 1449, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require

guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Second, the process of generating a peptide specific cytotoxic T cell requires the step of pulsing antigen presenting cells (APC) with the peptide consisting of SEQ ID NO: 1 wherein X represents histidine or arginine, coculturing said APC with CD4 depleted autologous PBMC, restimulating cytotoxic T cells weekly with the peptide and isolating minor antigen HA-1 specific cytotoxic T cells that are capable of HLA-A2.1 class I restricted VLHDDLLEA (SEQ ID NO: 2) or VLRDDLLEA (SEQ ID NO: 5) specific lysis of target cells.

Third, there is insufficient guidance as to which "suicide gene" is being transduced by the claimed process without the polynucleotide (claim 16).

Finally, given the unlimited number of minor antigen, there is insufficient working example demonstrating that the claimed process could produce cytotoxic T cell against all minor antigens by simply contacting hematopoetic cell with a peptide comprising the sequence VLXDDLLEA (SEQ ID NO: 1) wherein X represents histidine or arginine.

Miyazaki et al teach minor H antigen could be attractive targets for immunotherapy of solid tumors *only when* antigenic peptides are appropriately processed and presented by intact HLA class I molecules on tumor cells (see title, abstract, page 201, col. 2, in particular). Since the process for producing a cytotoxic T cell against all minor antigens is not enabled, it follows that any cytotoxic cells produced by said method is not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 12-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any peptide "comprising" the sequence VLXDDLLEA (SEQ ID NO: 1) wherein X represents histidine or arginine and (2) any "suicide gene" for the claimed process.

The specification discloses only two peptides of minor Histocompatibility antigen HA-1. The peptides are VLHDDLLEA (SEQ ID NO: 2) and VLRDDLLEA (SEQ ID NO: 5) wherein the peptides having a structure of nine amino acids in length for diagnosing incompatible minor Histocompatibility antigen HA-1 associated with bone marrow transplant and generating HA-1 specific CTLs ex-vivo. The specification further discloses a process of ex vivo induction of HA-I and HA-2 specific CTLs wherein the method comprises pulsed APC with HA- 1or HA-2 peptides, cultured APC and responder cells (CD4 depleted autologous PBMC) in 24 well culture plates, restimulated the T cell cultures weekly with peptide pulsed autologous monocytes (page 26).

With the exception of the specific peptide, there is insufficient written description about the structure associated with function of any peptide "comprising" the sequence VLXDDLLEA (SEQ ID NO: 1) because the term "comprising" is open-ended. It expands the peptide to include additional amino acids at either or both end. Further, there is inadequate written description about the structure of all "suicide gene" without the polynucleotide sequence for the claimed method of transducing the "suicide gene" into minor HA-1 antigen specific T cells.

The specification discloses only two peptides consisting of SEQ ID NO: 2 and 5 for a method of producing minor HA-1 antigen specific cytotoxic T cell, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide for cytotoxic T cell against *all* minor antigen, and a representative number of species of "suicide gene" to describe the genus of peptide and "suicide gene" for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claims 12-18 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: pulsing antigen presenting cells (APC) with the peptide consisting of SEQ ID NO: 1 wherein X represents histidine or arginine, coculturing said APC with CD4 depleted autologous PBMC, restimulating cytotoxic T cells weekly with the peptide and isolating minor antigen HA-1 specific cytotoxic T cells that are capable of HLA-A2.1 class I restricted VLHDDLLEA (SEQ ID NO: 2) or VLRDDLLEA (SEQ ID NO: 5) specific lysis of target cells.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 12-16 and 18-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bakker et al (Cancer Res 55(22): 5330-4, Nov 1995; PTO 892) in view of Goulmy et al (Human Immunology 54: 8-14, April 1997; PTO 892) and Van der Haan et al (Science 279(13): 1054-1.57, Feb 1998; PTO 1449) or Nagase et al (DNA Res 3(5): 321-329 (1996; PTO 1449).

Bakker et al teach a process of producing cytotoxic T cell against melanoma associated antigen, the process comprises providing peptide derived from melanocyte differentiation antigen to antigen presenting cells (APC) in the presence of peripheral blood monocytes (hematopoietic cell) and thus producing melanoma-associated antigen specific cytotoxic T cell in vitro or ex vivo (see abstract, in particular). Bakker et al teach CTLs are capable of recognizing naturally processed and presented epitopes and the ability to generate tumor peptide specific CTLs in vitro illustrates the potential used of these cells for vaccination protocols in human cancer (see abstract, in particular). The reference CTLs are capable of expansion in the presence of cytokines (see materials and methods, in particular).

The invention in claim 12 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen instead of melanocyte differentiation antigen by providing an isolated peptide comprising the sequence VLXDDLLEA (SEQ ID NO: 1) wherein X represents histidine or arginine.

The invention in claim 13 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen wherein the hematopoietic cell is negative for the minor antigen.

The invention in claim 14 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen is HA-1.

The invention in claim 16 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen further comprises transducing the cytotoxic T-cell with a suicide gene.

The invention in claim 19 differs from the teachings of the reference only in that a cytotoxic T cell produced by the process according to claim 12.

Goulmy et al teach cytotoxic T cells specific for minor histocompatibility antigen such as HA-1 is useful for adoptive immunotherapy as a treatment by eliminating refractory, residual or relapsed leukemia in patient (see page 12, col. 1, in particular). Goulmy et al teach the ideal situation is to generate minor antigen HA-1 peptide CTLs ex vivo from minor antigen negative bone morrow donors for minor antigen positive patients (See page 12, col. 1, in particular).

Goulmy et al further teach transduction of these CTLs with a suicide gene makes elimination of the CTL possible in case adverse effects occur (See page 12, col. 1, in particular).

Van der Haan et al teach minor histocompatibility antigen nanopeptides such as VLHDDLLEA and VLRDDLLEA that is 100 % identical to SEQ ID NO: 1 wherein X is histidine (H) or arginine (R) or about (see page 1056, col. 1, in particular) from HA-1 specific CTL clone (see page 1055, col. 3, in particular). Van der Haan et al further teach minor histocompatability HA-1 antigen comprising SEQ ID NO: 1 encoded by the cDNA sequence designated KIAA0223 (see page 1056, col. 1, in particular) as evident by GenBank accession number D86976. Van der Haan et al teach

Nagase et al teach an antigen comprising QCG...**VLRDDLLEA**...EFV (see enclosed underline sequence). The term "comprising" is open-ended. It expands the peptide in the claimed method to include additional amino acids at both ends to include the reference antigen.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute melanocyte differentiation antigen in the process for producing cytotoxic cell as taught by Bakker et al for the minor antigen HA-1 peptide such as VLHDDLLEA and VLRDDLLEA as taught by Van der Haan et al or the peptide as taught by Nagase et al for a method producing cytotoxic T cell against a minor antigen as taught by Bakker and Goulmy et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to produce cytotoxic T cell against minor antigen HA-1 because Goulmy et al teach cytotoxic T cells specific for minor histocompatibility antigen such as HA-1 can lyse leukemia cells expressing minor antigen and minor antigen specific CTL is useful for adoptive immunotherapy as a treatment by eliminating refractory, residual or relapsed leukemia in patient (see page 12, col. 1, in particular). Bakker et al teach CTLs are capable of recognizing naturally processed and presented epitopes and the ability to generate tumor peptide specific CTLs in vitro illustrates the potential used of these cells for vaccination protocols in human cancer (see abstract, in particular).

14. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bakker et al (Cancer Res 55(22): 5330-4, Nov 1995; PTO 892) in view of Goulmy et al (Human Immunology 54: 8-14, April 1997; PTO 892), Van der Haan et al (Science 279(13): 1054-1057, Feb 1998; PTO 1449) or Nagase et al (DNA Res 3(5): 321-329 (1996; PTO 1449) as applied to claims 12-16 and 18-20 mentioned above and further in view of Faller et al (J Virology 62(8): 2942-2950, August 1988; PTO 892).

The combined teachings of Bakker et al, Goulmy et al and Den Haan et al or Nagase et al and have been discussed supra.

The invention in claim 17 differs from the teachings of the reference only in that a process for producing cytotoxic T cell against a minor antigen wherein the cytotoxic T cell is immortalized.

Faller et al teach a process of producing immortalized cytotoxic T cell by infecting cytotoxic T cells with HTLV-1 virus and prolong survival of CTL in vitro in the absence of antigen stimulation without affecting the cytolytic capacity and antigen specificity of CTLs (see entire document, abstract, page 2943, col. 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to immortalized any cytotoxic T cell as taught by Faller with the cytotoxic T cell against minor HA antigen as taught by Bakker et al, Den Haan et al, Nagase et al and Goulmy et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to immortalized cytotoxic T cell against minor antigen HA-1 because Faller et al teach that these T cell clones proliferated indefinitely in culture and retained their cytotoxic capacity and antigen specificity (see page 2942, col. 2, first paragraph, in particular). Goulmy et al teach cytotoxic T cells specific for minor histocompatibility antigen such as HA-1 can lyse leukemia cells expressing minor antigen and minor antigen specific CTL is useful for adoptive immunotherapy as a treatment by eliminating refractory, residual or relapsed leukemia in patient (see page 12, col. 1, in particular).

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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January 7, 2005

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